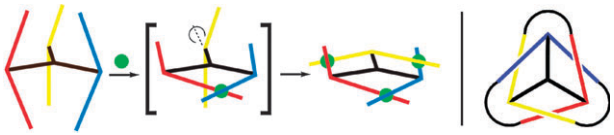
Synthesis of a D3-symmetric "trefoil" knotted cyclophane

Arias, Karla I ; Zysman-Colman, Eli ; Loren, Jon C ; Linden, Anthony ; Siegel, Jay S

DOI: https://doi.org/10.1039/C1CC11209K

Chemical Communications c1cc11209k



Q1 **Synthesis of a D_3-symmetric "trefoil" knotted cyclophane**

Karla I. Arias, Eli Zysman-Colman, Jon C. Loren, Anthony Linden and Jay S. Siegel*

Synthesis of a D_3-symmetric knotted cyclophane by cyclization of a D_3-symmetric tripodal tris-metal complex.

Please check this proof carefully. **Our staff will not read it in detail after you have returned it.** Translation errors between word-processor files and typesetting systems can occur so the whole proof needs to be read. Please pay particular attention to: tabulated material; equations; numerical data; figures and graphics; and references. If you have not already indicated the corresponding author(s) please mark their name(s) with an asterisk. Please e-mail a list of corrections or the PDF with electronic notes attached -- do not change the text within the PDF file or send a revised manuscript.

Please bear in mind that minor layout improvements, e.g. in line breaking, table widths and graphic placement, are routinely applied to the final version.

Please note that, in the typefaces we use, an italic vee looks like this: v, and a Greek nu looks like this: ν.

We will publish articles on the web as soon as possible after receiving your corrections; **no late corrections will be made.**

Please return your **final** corrections, where possible within **48 hours** of receipt, by e-mail to: chemcomm@rsc.org

Reprints—Electronic (PDF) reprints will be provided free of charge to the corresponding author. Enquiries about purchasing paper reprints should be addressed via: http://www.rsc.org/publishing/journals/guidelines/paperreprints/. Costs for reprints are below:

Reprint costs		
No of pages	Cost (per 50 copies)	
	First	Each additional
2-4	£225	£125
5-8	£350	£240
9-20	£675	£550
21-40	£1250	£975
>40	£1850	£1550
Cost for including cover of journal issue: £55 per 50 copies		

Queries are marked on your proof like this Q1, Q2, etc. and for your convenience line numbers are indicated like this 5, 10, 15, ...

Query reference	Query	Remarks
Q1	For your information: You can cite this article before you receive notification of the page numbers by using the following format: (authors), Chem. Commun., (year), DOI: 10.1039/c1cc11209k.	
Q2	In the sentence beginning 'Treatment of **13**. . .' 'clean formation of the desired templated knotted cyclophane **14'** is stated, however 'Synthesis of **1**' is stated in the caption to Scheme 2. Please indicate any changes that are required here	
Q3	The sentence beginning ''Synthesis of knotted metal. . .'' has been altered for clarity, please check that the meaning is correct.	
Q4	Ref. 8: Please provide the following details: volume number.	

ChemComm

Dynamic Article Links

Cite this: DOI: 10.1039/c1cc11209k

www.rsc.org/chemcomm

COMMUNICATION

Synthesis of a D_3-symmetric "trefoil" knotted cyclophane†

Karla I. Arias,[a] Eli Zysman-Colman,[b] Jon C. Loren,[c] Anthony Linden[a] and Jay S. Siegel*[a]

Received 28th February 2011, Accepted 4th May 2011
DOI: 10.1039/c1cc11209k

A D_3-symmetric knotted cyclophane, with a subgraph of trefoil topology, was synthesized by cyclization of a D_3-symmetric scaffold. Control of configuration at the three metal-based stereocenters arises from a bascule/pivot mechanism.

Complex topologies sophisticate life's macromolecules, provoke molecular architects and challenge stereochemical theory.[1,2] From Byzantine biopolymers[3] to concatenated coordination complexes,[4] these purely mathematical constructs find empircial expression as effigies of valence-bond-encoded molecular graphs. The taxonomy of topological stereochemistry focuses on three fundamental classes: links, knots and "non-planar" graphs.[5] Each structure requires an entwinement wherein entropy disfavors a stochastic selection. The most successful synthetic strategies toward topological targets employ templating effects like metal coordination,[6,7] charge-transfer stacking,[8] and hydrogen-bonding templates,[9] each of which has led to trefoil knotted molecules of various symmetries. A metal-directed approach *via* a D_3-symmetrical scaffold offers a strategy to a D_3-symmetrical knotted cyclophane with high stereoselectivity.

The retrosynthesis of the knotted cyclophane is easily visualized (Fig. 1). Key challenges include: (a) configurational (over–under) control of the metal-based stereocenters, (b) construction of the crescent-shaped pivot arms, and (c) installation of the peripheral linkers capable of closing the circuit and completing the knotted architecture. To control the configuration of the metal-coordinating stereocenters, a template was designed comprising three bis-bipyridylphenyl pivot arms centrally connected *via* alkyne spacers to a rigid benzene core.

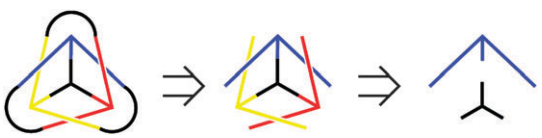
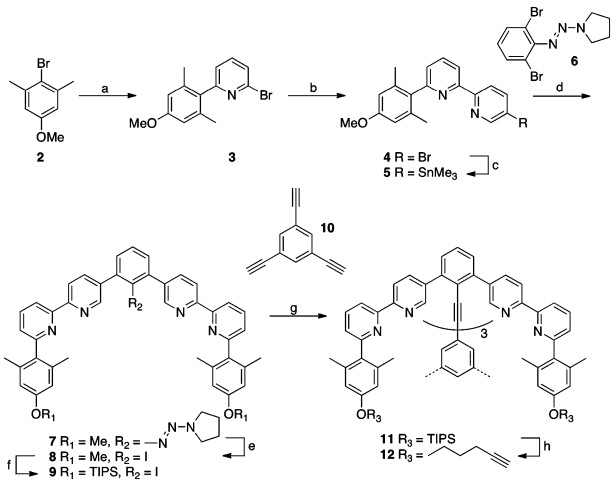


Fig. 1 Schematic retrosynthesis of a D_3-symmetrical knotted cyclophane.

Initial coordination of a metal ion, like copper(I), by ligands of neighboring pivot arms sets the configuration about the metal-centered stereocenter and then a cantilever mechanism dictates the overall configuration at the remaining metal-based stereocenters; when one side of the pivot arm moves down to coordinate to a metal, the other moves up. The result is the formation of a D_3-symmetric complex.[10]

Synthesis of **12** results from a manifold use of palladium-catalyzed cross-coupling reactions (Scheme 1). Bipyridine **4** comes *via* two successive Negishi couplings.[11] Palladium catalyzed conversion of **4** to stannane **5** proceeds in excellent yield, albeit with stoichiometric amounts of hexamethylditin.[12] Two equivalents of **5** couple well to dibromophenyltriazine **6** under optimized Stille conditions, to form **7**, which precipitates out of solution.[13] After filtration, crescent **7** is converted



Scheme 1 Synthesis of **12** [yield]: (a) 1. *n*BuLi/THF, −78 °C, 40 min, 2. $ZnCl_2$/THF, −78–0 °C, 1 h, 3. 1 equiv. 2,6-dibromopyridine, 1.5 mol% $Pd(PPh_3)_4$/THF, reflux, 18 h [83%]; (b) 1. *n*BuLi/THF, −78 °C, 40 min, 2. $ZnCl_2$/THF, −78–0 °C, 1 h, 3. 1 equiv. 2,5-dibromopyridine, 1.5 mol% $Pd(PPh_3)_4$/THF, reflux, 18 h [48%]; (c) $(SnMe_3)_2$, 2 mol% $Pd(PPh_3)_4$/DME, reflux, 5.5 h [92%]; (d) 0.5 equiv. **6**, 10 mol% $Pd(PPh_3)_4$/toluene, reflux, 18 h [83%]; (e) 2 equiv. I_2/$ClCH_2CH_2Cl$, reflux, 48 h [96%]; (f) 47% HI (aq.), reflux, 16 h, // 3 equiv. TIPSOTf/CH_2Cl_2, NEt_3, −78–0 °C, 14 h [88%]; (g) 0.3 equiv. **10**, 10 mol% $Pd(PPh_3)_4$/1 : 1 NEt_3 : toluene, reflux, 18 h [70%]; (h) 1. 6.6 equiv. TBAF/THF, −78 °C—RT, 4 h, 2. 6.6 equiv. pent-4-ynyl toluenesulfonate, 20 equiv. Cs_2CO_3/DMF, 85 °C, 18 h [95%].

[a] *Organisch-chemisches Institut, Universität Zürich, Winterthurerstrasse 190, 8057, Zürich, Switzerland. E-mail: jss@oci.uzh.ch; Fax: +41 44-635-6888*
[b] *Faculté des Sciences, Université de Sherbrooke, 2500 Blvd de l'Université, Sherbrooke J1K 2R1, Canada*
[c] *Dept of Medicinal Chemistry, The Genomics Institute of the Novartis Research Foundation, 10675 John Jay Hopkins Dr, San Diego, CA 92121, USA*

† Electronic supplementary information (ESI) available: 67 Pages of procedures, data and spectra. CCDC 779280. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c1cc11209k

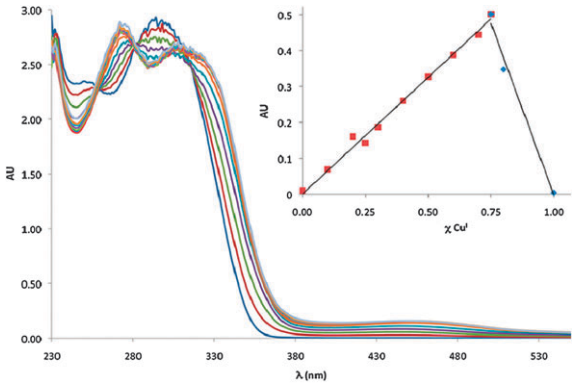


Fig. 2 UV/Vis spectral titration of $Cu^{I}(MeCN)_4PF_6$ with **12** in CH_2Cl_2. Inset: Job Plot for $Cu^{I}(MeCN)_4PF_6$ *vs.* **12** at 450 nm in CH_2Cl_2.

to the corresponding iodo-crescent (**8**) with iodine in refluxing 1,2-dichloroethane.[14]

Manisyl groups improved the solubility compared to anisyl groups, making it easier to work with **8–12**.[15] Deprotection of **8** in refluxing 47% HI (aq) and subsequent reprotection as the triisopropylsilyl (TIPS) ether formed **9** (two steps). Copper-free Sonogashira coupling of **9** with **10** (3 equiv.) afforded **11**,[16] and *in situ* desilylation/alkylation of **11** crafted **12** [9 steps, 17% yield].[17]

A Job plot of mole fraction **12** *vs.* $Cu^{I}(MeCN)_4PF_6$ at 450 nm displays a sharp maximum at a Cu^{I} : **12** molar ratio of 3 : 1, supporting one Cu^{I} per site (Fig. 2). Such a sharp maximum suggests strong binding in favor of the 3 : 1 complex; however, titration of **12** with $Cu^{I}(MeCN)_4PF_6$ does not show clean isosbestic behavior. With the addition up to 1.5 equiv. of Cu^{I} to **12**, the absorption curves share isosbestic points at 260, 281, and 315 nm. From 2 to 2.5 equiv. of Cu^{I}, the absorption curves share isosbestic points at 256, 277, 300, and 359 nm. Beyond 3 equiv. of Cu^{I}, the curves are constant. This behavior suggests the presence of at least two intermediate bound states in solution.[18] The values of the stability and formation constants of the tri Cu^{I} complex were determined from the UV/Vis spectra (Table 1),[19] and indicate that the formation of **13** from Cu^{I} and **12** is at best weakly cooperative.

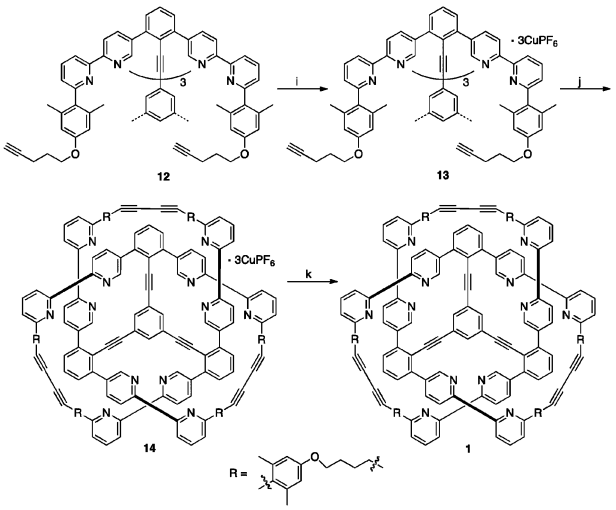
Treatment of **13** with excess $Cu^{II}(OAc)_2{\cdot}H_2O$ in refluxing CH_3CN[20] results in the clean formation of the desired templated knotted cyclophane **14** in excellent yield (Scheme 2). Formation of the desired product was deduced from ESIMS data, plus the loss of the terminal alkyne signals in both the IR and ^1H NMR spectra. (Fig. 3).

Dark red crystals were grown from vapor diffusion of ether into a nitromethane solution of the hexafluorophosphate salt of **14**; crystal structure determination unequivocally confirmed the formation of the desired knotted structure, which possesses the correct topology and connectivity (Fig. 4).[21] The formally

Table 1 Stability constants of $CuI(MeCN)_4PF_6$ into **12**

$\log K_1$	$\log K_2$	$\log K_3$	$\log \beta_2$	$\log \beta_3$
6.54(0)	4.33(9)	5.50(0)	10.88(0)	16.38(2)

Calculated using ReactLab Equilibria from UV/Vis spectra in CH_2Cl_2.



Scheme 2 Synthesis of **1**. (i) 3 equiv. $Cu^{I}(MeCN)_4PF_6$/1 : 1 NEt_3 : CH_2Cl_2, RT, 2 h [95%]; (j) 36 equiv. $Cu(OAc)_2{\cdot}H_2O/CH_3CN$, reflux, 16 h [85%]; (k) 20% KCN (aq.)/CH_2Cl_2, RT, 2 h [91%].

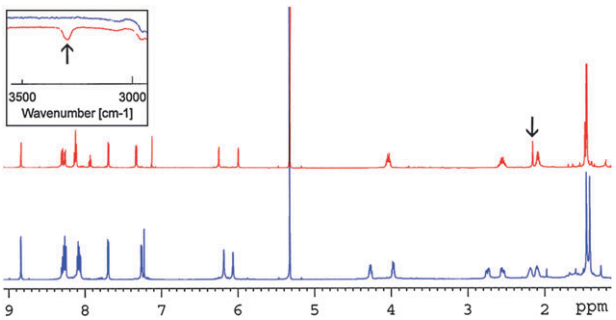


Fig. 3 600 MHz ^1H NMR of **13** (red) and **14** (blue) in CD_2Cl_2. (ref. 5.32 ppm from $CHDCl_2$). Inset: IR of **13** (red) and **14** (blue). Black arrows indicate the terminal alkyne signal in **13**.

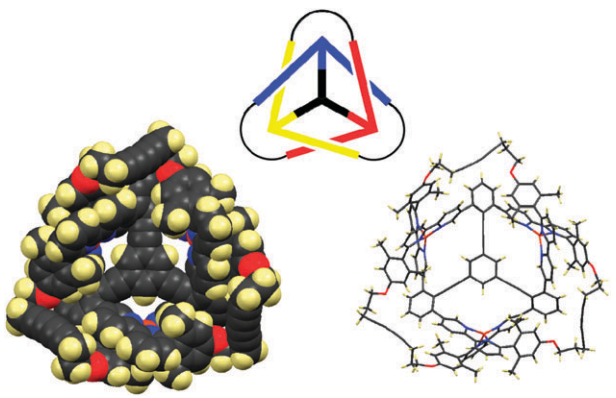


Fig. 4 Crystal structure of **14**: (left) spacefilling; (right) capped-stick.

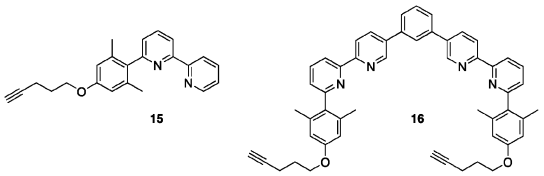
D_3 knotted cyclophane **14** packs with crystallographic C_3 symmetry. It displays three Cu^{I} centers at the vertices of an equilateral triangle of edge length *ca.* 10.9 Å. Further analysis of the crystal structure reveals that the knotted copper-complexed cyclophane crystallizes as a racemate within a cubic crystal system (space group: $P3n$). Synthesis of knotted metal-free cyclophane **1** was achieved by the removal of the copper with an aqueous solution of KCN.

Table 2 Absorption and emission maxima, molar absorptivity values ($\log \varepsilon$), quantum yields (ϕ_f), and lifetimes (τ_f)

	UV/Vis[a]		Fluorescence[ab]		
	λ_{abs}/nm	$\log \varepsilon$/cm^{-1} mol^{-1} L	λ_{em}/nm	ϕ_f	τ_f/ns
15	283	4.19	370	0.04	1.63
16	310	4.73	372	0.08	2.58
12	297	5.15	375	0.31	2.79
1	293	5.03	373	0.20	3.02

[a] All values measured in CH_2Cl_2. [b] PPO in cyclohexane (ϕ_f = 0.94) was the standard;[22] the emission maxima values were obtained at 75% height.

The photophysical properties of reference compounds **15**, **16** and **12** showed an increase in the molar absorptivity, quantum yield, and lifetime in CH_2Cl_2 across the series. The behavior of **12** most closely matches that of **1** (Table 2).



Synthesis of a D_3-symmetric knotted cyclophane was achieved by the cyclization of the alkynyl-capped intermediate **12** using the Eglinton protocol. The desired over–under arrangement is controlled by means of a cantilever mechanism to complex Cu^I ions to the crossed polypyridine arm in **11**. Completion of the trefoil knot synthesis still requires the cleavage of the central triethynylbenzene scaffold.

Notes and references

1 (*a*) L. F. Liu, R. E. Depew and J. C. Wang, *J. Mol. Biol.*, 1976, **106**, 439–452; (*b*) L. F. Liu, C.-C. Liu and B. M. Alberts, *Cell*, 1980, **19**, 697–707; (*c*) S. E. Wasserman, J. M. Dungan and N. R. Cozzarelli, *Science*, 1985, **229**, 171–174; (*d*) S. E. Wasserman and N. R. Cozzarelli, *Science*, 1986, **232**, 951–960; (*e*) S. Trigueros, J. Arsuaga, M. E. Vazquez, D. W. Sumners and J. Roca, *Nucleic Acids Res.*, 2001, **29**, 67–71.

2 (*a*) C. Liang and K. Mislow, *J. Am. Chem. Soc.*, 1994, **116**, 11189–11190; (*b*) O. Nureki, M. Shirouzu, K. Hashimoto, R. Ishitani, T. Terada, M. Tamakoshi, T. Oshima, M. Chijimatsu, K. Takio, D. G. Vassylyev, T. Shibata, Y. Inoue, S. Kuramitsu and S. Yokoyama, *Acta Crystallogr., Sect. D*, 2002, **58**, 1129–1137; (*c*) T. I. Zarembinski, Y. Kim, K. Peterson, D. Christendat, A. Dharamsi, C. H. Arrowsmith, A. M. Edwards and A. Joachimiak, *Proteins: Struct., Funct., Genet.*, 2003, **50**, 177–183; (*d*) W. Taylor, *Nature*, 2000, **406**, 916–919; (*e*) C. Liang and K. Mislow, *J. Am. Chem. Soc.*, 1995, **117**, 4201–4214; (*f*) G. Schill, G. Doerjer, E. Logemann and H. Fritz, *Chem. Ber.*, 1979, **112**, 3603–3615.

3 (*a*) J. E. Mueller, S. M. Du and N. C. Seeman, *J. Am. Chem. Soc.*, 1991, **113**, 6306–6308; (*b*) J. Chen and N. C. Seeman, *Nature*, 1991, **350**, 631–633; (*c*) For a representative review, see: N. C. Seeman, *Angew. Chem., Int. Ed.*, 1998, **37**, 3220–3238; (*d*) M. Feigel, R. Ladberg, S. Engels, R. Herbst-Irmer and R. Fröhlich, *Angew. Chem., Int. Ed.*, 2006, **45**, 5698–5702.

4 C. O. Dietrich-Buchecker, J.-P. Sauvage and J. P. Kintzinger, *Tetrahedron Lett.*, 1983, **24**, 5095–5098; C. O. Dietrich-Buchecker, B. Colasson, M. Fujita, A. Hori, N. Geum, S. Sakamoto, K. Yamaguchi and J.-P. Sauvage, *J. Am. Chem. Soc.*, 2003, **125**, 5717–5725.

5 D. M. Walba, *Tetrahedron*, 1985, **41**, 3161–3212.

6 (*a*) C. O. Dietrich-Buchecker and J.-P. Sauvage, *Angew. Chem., Int. Ed. Engl.*, 1989, **28**, 189–192; (*b*) C. O. Dietrich-Buchecker, J. Guilhem, C. Pascard and J.-P. Sauvage, *Angew. Chem., Int. Ed. Engl.*, 1990, **29**, 1154–1156; (*c*) C. O. Dietrich-Buchecker, G. Rapenne and J.-P. Sauvage, *Chem. Commun.*, 1997, 2053–2054; (*d*) C. O. Dietrich-Buchecker, G. Rapenne, J.-P. Sauvage, A. De Cian and J. Fischer, *Chem.–Eur. J.*, 1999, **5**, 1432–1439; (*e*) G. Rapenne, C. O. Dietrich-Buchecker and J.-P. Sauvage, *J. Am. Chem. Soc.*, 1999, **121**, 994–1001.

7 For the original proposal of a trefoil knot synthesis based on an octahedral metal template, see: (*a*) V. I. Sokolov, *Russ. Chem. Rev.*, 1973, **42**, 452–463; (*b*) H. Adams, E. Ashworth, G. A. Breault, J. Guo, C. A. Hunter and P. C. Mayers, *Nature*, 2001, **411**, 763–764; (*c*) J. Guo, P. C. Mayers, G. A. Breault and C. A. Hunter, *Nat. Chem.*, 2010, **2**, 218–222.

8 P. R. Ashton, O. A. Matthews, S. Menzer, F. M. Raymo, N. Spencer, J. F. Stoddart and D. J. Williams, *Liebigs Ann. Chem.*, 1997, 2485–2494.

9 (*a*) O. Safarowsky, M. Nieger, R. Fröhlich and F. Vögtle, *Angew. Chem., Int. Ed.*, 2000, **39**, 1616–1618; (*b*) F. Vögtle, A. Hünten, E. Vogel, S. Buschbeck, O. Safarowsky, J. Recker, A.-H. Parham, M. Knott, W. M. Müller, U. Müller, Y. Okamoto, T. Kubota, W. Lindner, E. Francotte and S. Grimme, *Angew. Chem., Int. Ed.*, 2001, **40**, 2468–2471; (*c*) O. Lukin, J. Recker, A. Böhmer, W. M. Müller, T. Kubota, Y. Okamoto, M. Nieger, R. Fröhlich and F. Vögtle, *Angew. Chem., Int. Ed.*, 2003, **42**, 442–445; (*d*) For a review of the work done in the Vögtle lab, see: O. Lukin and F. Vögtle, *Angew. Chem., Int. Ed.*, 2005, **44**, 1456–1477.

10 C. R. Woods, M. Benaglia, S. Toyota, K. Hardcastle and J. S. Siegel, *Angew. Chem., Int. Ed.*, 2001, **40**, 749–751.

11 (*a*) E. Negishi, *J. Org. Chem.*, 1977, **42**, 1821–1823; (*b*) E. Negishi and T. Takahashi, *Org. Synth.*, 1988, **66**, 67–74.

12 M. Benaglia, S. Toyota, C. R. Woods and J. S. Siegel, *Tetrahedron Lett.*, 1997, **38**, 4737–4740.

13 J. K. Stille, *Angew. Chem., Int. Ed. Engl.*, 1986, **25**, 508–524.

14 Z. Wu and J. S. Moore, *Tetrahedron Lett.*, 1994, **35**, 5539–5542.

15 Manisole = 3,5-dimethylanisole; manisyl = 4-methoxy-2,6-dimethylphenyl; J. C. Loren and J. S. Siegel, *Angew. Chem., Int. Ed.*, 2001, **40**, 754–757.

16 S. Takahashi, Y. Kuroyama, K. Sonogashira and N. Hagihara, *Synthesis*, 1980, 627–630.

17 Attempts to form the knotted cyclophane from the deprotected tricopper(I) complex suffered from poor solubility.

18 (*a*) D. C. Harris, in, *Quantitative Chemical Analysis*, W. H. Freeman and Company, New York, Fourth edn, 1995; (*b*) T. E. Glass, *J. Am. Chem. Soc.*, 2000, **122**, 4522–4523.

19 P. King and M. Maeder, *ReactLab Equilibria*, Jplus Consulting Pty Ltd, 2011.

20 P. Siemsen, R. C. Livingston and F. Diederich, *Angew. Chem., Int. Ed.*, 2000, **39**, 2632–2657.

21 Crystal data for compound **1**: red crystals from CH_3NO_2, *Nonius KappaCCD* diffractometer, $[Cu_3(C_{168}H_{132}N_{12}O_6)](PF_6)_3$, M = 3040.5, cubic, a = 33.7312(6) Å, V = 38379(1) Å^3, T = 160(1) K, space group P-43n, Z = 8, μ(Mo-Kα) = 0.420 mm^{-1}, 153 129 reflections measured, 7819 unique reflections, 4112 reflections with $I > 2\sigma(I)$. The available crystals were of poor quality and were possibly not true single crystals. The best refinement yielded $R(F)$ = 0.21. The connectivity and gross topology of the cation are clearly defined, but the geometric parameters should be considered as approximate. The presence of additional solvent molecules in the structure cannot be excluded. CCDC 779280 contains the supplementary crystallographic data for this communication.

22 N. Boens, W. Qin, N. Basaric, J. Hofkens, M. Ameloot, J. Pouget, J.-P. Lefevre, B. Valeur, E. Gratton, M. vandeVen, N. D. Silva, Y. Engelborghs, K. Willaert, A. Sillen, G. Rumbles, D. Phillips, A. Visser, A. van Hoek, J. R. Lakowicz, H. Malak, I. Gryczynski, A. G. Szabo, D. T. Krajcarski, N. Tamai and A. Miura, *Anal. Chem.*, 2007, **79**, 2137–2149.